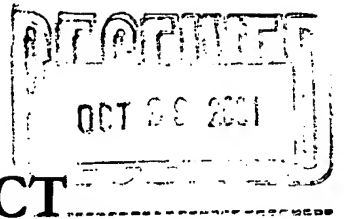


PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To: JANE MASSEY LICATA
LICATA & TYRRELL
66 E. MAIN STREET
MARLTON NJ 08053

Docket System ☒
Status Report ☒
Docket Book ☒

NP = 3/9/02

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

26 OCT 2001

Applicant's or agent's file reference

RTSP-0048

IMPORTANT NOTIFICATION

International application No.

PCT/US00/00583

International filing date (day/month/year)

10 JANUARY 2000

Priority Date (day/month/year)

09 SEPTEMBER 1999

Applicant

ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

KAREN LACOURCIERE

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

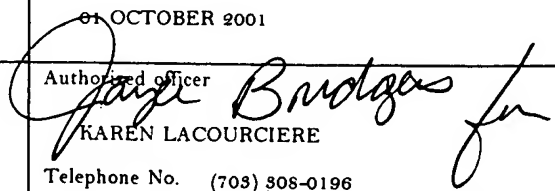
Applicant's or agent's file reference RTSP-0048	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/00583	International filing date (day/month/year) 10 JANUARY 2000	Priority date (day/month/year) 09 SEPTEMBER 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 05 APRIL 2001	Date of completion of this report 01 OCTOBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  KAREN LACOURCIERE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the claims:
pages 82 and 83 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____
- ☒ the sequence listing part of the description:
pages 1-12 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>3-20</u>	YES
	Claims	<u>1 and 2</u>	NO
Inventive Step (IS)	Claims	<u>3, 4, and 16-20</u>	YES
	Claims	<u>1, 2, and 5-15</u>	NO
Industrial Applicability (IA)	Claims	<u>1-20</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by WO 98/35693 (UNIVERSITY OF OTTOWA).

WO 98/35693 discloses nucleic acid sequences encoding XIAP, which is equivalent to the instant X-linked inhibitor of apoptosis, and disclose, at pages 13 and 14 for example, regions of such a nucleic acid targetable by antisense and preferred antisense lengths such as 8-25 nucleotides. Example 9 and page 45 disclose that antisense to XIAP have been made and tested.

Claims 5-15 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Cook S.T. (Antisense Medicinal Chemistry. In: Antisense Research and Application. 1998, pages 69-76). The instant invention comprises various chemical modifications to antisense oligonucleotides targeted to XIAP. WO 98/35693 disclose antisense targeted to XIAP. Cook discloses various modifications that are used in antisense oligonucleotides which one would use for the various benefits recognized in the art for such modifications to antisense oligonucleotides.

Claims 3, 4, and 16-20 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides recited in claims 3 and 4 nor does the art teach or fairly suggest methods of treating disease with antisense oligonucleotides targeted to X-linked Inhibitor of Apoptosis (XIAP).

_____ NEW CITATIONS _____

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

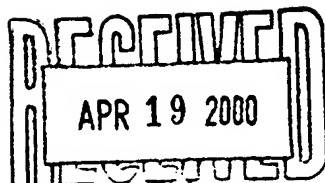
Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US Cl.: 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44



PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

LICATA, Jane, Massey
Law Offices of Jane Massey Licata
66 E. Main Street
Marlton, NJ 08053
ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 07 April 2000 (07.04.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference RTSP-0048	
International application No. PCT/US00/00583	International filing date (day/month/year) 10 January 2000 (10.01.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 09 September 1999 (09.09.99)
Applicant ISIS PHARMACEUTICALS, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
09 Sept 1999 (09.09.99)	09/392,580	US	28 Marc 2000 (28.03.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

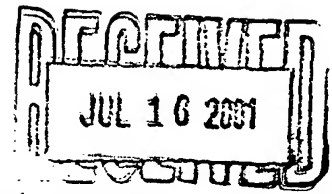
Facsimile No. (41-22) 740.14.35

Authorized officer

Tessadel PAMPLIEGA *Tdp*

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: JANE MASSEY LICATA LICATA & TYRRELL 66 E. MAIN STREET MARLTON NJ 08053 <div style="text-align: right;"> Docket System <input checked="" type="checkbox"/> Status Report <input checked="" type="checkbox"/> Docket Book <input checked="" type="checkbox"/> 9/12/01 WO </div>			Date of Mailing (day/month/year) 12 JUL 2001		
Applicant's or agent's file reference RTSP-0048			REPLY DUE within TWO months from the above date of mailing		
International application No. PCT/US00/00583		International filing date (day/month/year) 10 JANUARY 2000		Priority date (day/month/year) 09 SEPTEMBER 1999	
International Patent Classification (IPC) or both national classification and IPC Please See Supplemental Sheet.					
Applicant ISIS PHARMACEUTICALS, INC.					

1. This written opinion is the <u>first</u> (first, etc.) drawn by this International Preliminary Examining Authority.	
2. This opinion contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step or industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 	
3. The applicant is hereby invited to reply to this opinion. <div style="margin-top: 10px;"> <p>When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).</p> <p>How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.</p> <p>Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.</p> <p>If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.</p> </div>	
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09 JANUARY 2002	

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <div style="text-align: center;"> SEAN MCGARRY </div> Telephone No. (703) 308-0196
--	---

WRITTEN OPINION

International application No.

PCT/US00/00583

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed
☒ the description:
 pages 1-81, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

☒ the claims:
 pages 82 and 83, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

☒ the drawings:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

☒ the sequence listing part of the description:
 pages 1-12, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

WRITTEN OPINION

International application No.

PCT/US00/00583

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	3-20	YES
	Claims	1 and 2	NO
Inventive Step (IS)	Claims	3, 4, and 16-20	YES
	Claims	1, 2, and 5-15	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by WO 98/35693 (UNIVERSITY OF OTTOWA).

WO 98/35693 discloses nucleic acid sequences encoding XIAP, which is equivalent to the instant X-linked inhibitor of apoptosis, and disclose, at pages 13 and 14 for example, regions of such a nucleic acid targetable by antisense and preferred antisense lengths such as 8-25 nucleotides. Example 9 and page 45 disclose that antisense to XIAP have been made and tested.

Claims 5-15 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Cook S.T. (Antisense Medicinal Chemistry. In: Antisense Research and Application. 1998, pages 69-76). The instant invention comprises various chemical modifications to antisense oligonucleotides targeted to XIAP. WO 98/35693 disclose antisense targeted to XIAP. Cook discloses various modifications that are used in antisense oligonucleotides which one would use for the various benefits recognized in the art for such modifications to antisense oligonucleotides.

Claims 3, 4, and 16-20 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides recited in claims 3 and 4 nor does the art teach or fairly suggest methods of treating disease with antisense oligonucleotides targeted to X-linked Inhibitor of Apoptosis (XIAP).

NEW CITATIONS
NONE

WRITTEN OPINION

International application No.

PCT/US00/00583

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

WRITTEN OPINION

International application No.

PCT/US00/00583

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US Cl.: 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/00583

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68

US CL : 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, MEDLINE BIOSIS, EMBASE, CAPLUS, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/35693 A2(UNIVERSITY OF OTTOWA) 20 August 1998, pages 13-14, 45 and Example 9.	1, 2
Y		5-15
Y	COOK S.T. Antisense Medicinal Chemistry. In: Antisense Research and Application. Edited by Stanley Crooke. New York: Springer. 1998, pages 69-76, entire document.	5-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

08 MARCH 2000

Date of mailing of the international search report

29 MAR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SEAN MCGARRY

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION

(PCT Article 36 and Rule 70)

14

REC'D 30 OCT 2001

REPORT PCT

Applicant's or agent's file reference RTSP-0048	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/00588	International filing date (day/month/year) 10 JANUARY 2000	Priority date (day/month/year) 09 SEPTEMBER 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

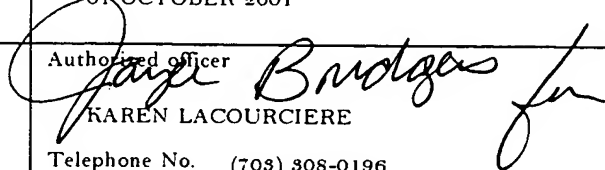
2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 05 APRIL 2001	Date of completion of this report 01 OCTOBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  KAREN LACOURCIERE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed
☒ the description:
pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

- ☒ the claims:
pages 82 and 83 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

- ☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

- ☒ the sequence listing part of the description:
pages 1-12 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims	<u>3-20</u>	YES
	Claims	<u>1 and 2</u>	NO
Inventive Step (IS)	Claims	<u>3, 4, and 16-20</u>	YES
	Claims	<u>1, 2, and 5-15</u>	NO
Industrial Applicability (IA)	Claims	<u>1-20</u>	YES
	Claims	<u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1 and 2 lack novelty under PCT Article 33(2) as being anticipated by WO 98/35693 (UNIVERSITY OF OTTOWA).

WO 98/35693 discloses nucleic acid sequences encoding XIAP, which is equivalent to the instant X-linked inhibitor of apoptosis, and disclose, at pages 13 and 14 for example, regions of such a nucleic acid targetable by antisense and preferred antisense lengths such as 8-25 nucleotides. Example 9 and page 45 disclose that antisense to XIAP have been made and tested.

Claims 5-15 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Cook S.T. (Antisense Medicinal Chemistry. In: Antisense Research and Application. 1998, pages 69-76). The instant invention comprises various chemical modifications to antisense oligonucleotides targeted to XIAP. WO 98/35693 disclose antisense targeted to XIAP. Cook discloses various modifications that are used in antisense oligonucleotides which one would use for the various benefits recognized in the art for such modifications to antisense oligonucleotides.

Claims 3, 4, and 16-20 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific antisense oligonucleotides recited in claims 3 and 4 nor does the art teach or fairly suggest methods of treating disease with antisense oligonucleotides targeted to X-linked Inhibitor of Apoptosis (XIAP).

----- NEW CITATIONS -----
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/00583

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US Cl.: 536/23.1, 24.1, 24.5; 435/6, 37
455; 514/44